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ARTICLE

# Evaluation of cardiovascular disease risk in individuals with chronic spinal cord injury

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## Abstract

**Study design** Multicentre, cross-sectional study.

**Objectives** To identify which markers of obesity, injury characteristics and autonomic function variables are related to cardiovascular disease (CVD) risk after spinal cord injury (SCI), and establish cut-points for detection and risk management.

**Setting** Eight SCI rehabilitation centres in the Netherlands.

**Methods** Individuals ( $n = 257$ ) with a traumatic, chronic ( $\geq 10$  years) SCI, with age at injury between 18 and 35 years, completed a self-report questionnaire and a one-day visit to a rehabilitation centre for testing. Three anthropometric measures were tested: body mass index (BMI); waist circumference (WC); and waist-to-height ratio (WHtR). Injury characteristics included: American Spinal Injury Association impairment scale (AIS); duration of injury (DOI); and neurological level of injury (LOI). Cardiovascular autonomic function was assessed from peak heart rate during maximal exercise ( $HR_{peak}$ ). Systolic arterial pressure (SAP) and aerobic capacity ( $VO_{2peak}$ ) were also determined. CVD risk was calculated using the Framingham risk score (FRS).

**Results** All anthropometric variables were associated with FRS, with WC showing the strongest correlation ( $r = 0.41$ ,  $p < 0.001$ ) and greatest area under the curve (0.73) for 10-year CVD risk (%). WC, DOI, SAP,  $HR_{peak}$ , LOI, and  $VO_{2peak}$  (variable importance: 0.81, 1.0, 0.98, 0.98, 0.66, 0.68, respectively) were important predictive variables for 10-year CVD risk in individuals with SCI.

**Conclusions** We confirm that WC is a simple, practical measure of CVD risk, and along with DOI and markers of cardiovascular autonomic function, plays a role in the increased CVD risk following SCI.

## Introduction

There are currently an estimated 4 million individuals living with the devastating consequences of a spinal cord injury

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(SCI) worldwide, with an average of 750,000 new cases each year [1]. SCI is more common in males (~76% of the SCI population) [2]. With advances in acute care and chronic management, the average age of individuals living with SCI (51 years) is increasing [2], and cardiovascular disease (CVD) is now the leading cause of morbidity and mortality among individuals with SCI [3], similar to the able-bodied population [4]. However, CVD is reported to occur earlier and progress more rapidly in individuals with SCI than in the able-bodied [5].

SCI disrupts sensory, motor, and autonomic pathways, with higher, more complete injuries resulting in greater loss of sensorimotor function [6] and increasing autonomic impairment [7]. The impairments in autonomic function are particularly pertinent in terms of CVD risk, as disruption to descending cardiovascular autonomic pathways impairs cardiovascular control of blood pressure and heart rate (HR), particularly in those with injuries at or above the sixth thoracic vertebra (T6) [8, 9]. These high-level autonomically-complete lesions are characterised by blood pressure instability [10], cardiac arrhythmia [11], and an inability to increase HR appropriately during exercise [12]. These numerous cardiovascular autonomic impairments have a devastating impact on quality of life [13], are consistently rated as a priority for improvement by individuals living with SCI [14], and are associated with an increased risk of CVD [15–17].

The repercussions of impaired autonomic function in this population are profound and affect multiple systems, negatively impacting traditional CVD risk factors, while possibly introducing new ones. Following SCI the prevalence of obesity is increased, likely from reduced physical activity [18], increased sedentary time [17], and decreased lean muscle mass [19], although alterations in metabolism [20] and gastrointestinal function [21] may also contribute. In those with autonomic impairment, increases in adiposity are commonly located around the viscera [22], which has a particularly poor prognosis in terms of CVD risk [23].

Given the high CVD burden after SCI, there is considerable interest in optimising assessment tools for the evaluation of CVD risk following injury, to ensure they are appropriate for this population. Given the known association between obesity and CVD risk, measures of adiposity are common screening tools. While body mass index (BMI) remains the ‘gold standard’ measurement for the general population, it underestimates obesity in those with SCI [24]. From a practical standpoint, waist circumference (WC) provides several measurement advantages in an SCI population—eliminating the need for specialised wheelchair scales to determine weight, and avoiding the difficulties, brought by spasticity and contractures, of recording height or length. In addition, WC is more strongly correlated with visceral adipose tissue in the SCI population than BMI [22]. There are promising preliminary data supporting the use of

WC, and perhaps waist-to-height ratio (WHtR), as valid measures of obesity-related CVD risk in individuals with SCI [25]. However, these need to be confirmed in larger cohorts. In addition, the impact of sex and injury characteristics on obesity-related CVD and the development of SCI-specific cut-points for obesity-related CVD are lacking.

Accordingly, we aimed to identify which metrics of obesity, injury characteristics and cardiovascular autonomic function variables are related to CVD risk (determined using the Framingham risk score [FRS]) in individuals with chronic traumatic SCI. We also aimed to establish SCI-specific cut-points for increased CVD risk based on individual and injury characteristics, to aid identification of individuals “at-risk” for CVD and assist health care providers when considering risk management.

## Methods

This study is part of the Dutch multicentre research programme “Active Lifestyle Rehabilitation Interventions in aging Spinal Cord injury (ALLRISC)”, a cross-sectional study of individuals with long-term SCI living in the Netherlands [26]. This study was approved by the Medical Ethics Committee of the University Medical Center Utrecht and the Department of Research Ethics at Simon Fraser University. Investigations were performed in accordance with the Declaration of Helsinki of the World Medical Association [27]. All participants gave written informed consent prior to participation.

## Participants

Individuals using a wheelchair (hand-rim or electric) with a traumatic, chronic ( $\geq 10$  yrs) SCI with age at injury between 18–35 years were included in the study. These criteria were applied to limit the confounding effects of age-related comorbidities and reduce the impact of CVD risk factors present prior to injury.

## Procedures

Study participants completed a 1-day evaluation that included an extensive medical assessment, physical examination, oral interview and several physical tests. Two weeks prior to the visit, participants completed a self-report questionnaire. On the testing day, participants were asked to fast (except for water) for 12 h prior to testing, refrain from vigorous exercise, and ensure appropriate bladder and bowel care was performed to minimise the likelihood of autonomic dysreflexia (AD, hypertensive episodes triggered by sensory stimuli arising from below the level of the lesion) during testing in susceptible individuals.

## Personal characteristics

Age, sex, and smoking status were extracted from the self-report questionnaire. Participant weight was determined by weighing participants in their wheelchair on a weigh bridge, and then subtracting the weight of the wheelchair. Participants reported their own height. BMI was calculated as weight divided by height squared ( $\text{kg} \cdot \text{m}^{-2}$ ). WC was measured in cm in the supine position, at the narrowest part of the waist after a normal expiration, using a stretch-resistant measuring tape. This approach was used because it is a standard approach, and because of its ease of applicability to the at-home and clinical arena, while recognising that other sites commonly used for determination of WC provide slightly different data, particularly in women [28]. WHtR was determined by dividing the measured WC by the self-reported height. Medication use was noted (Supplementary Table 1).

## Injury characteristics

Duration of injury (DOI) was extracted from the self-report questionnaire. A physiatrist determined the neurological level and severity of injury according to the International Standards for Neurological Classification of SCI [6]. A complete lesion was defined as the absence of motor and sensory function in the sacral segments, and classified as American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade A. AIS grades B, C, and D were classified as incomplete lesions. In addition to using neurological level of injury (LOI) linearly ( $C1 = 1$ ,  $C2 = 2$ , etc.), LOI was categorised according to three groups based on the known impact of LOI on cardiovascular autonomic pathways: C1–C8 levels were defined as “high” injuries (potential loss of autonomic control of cardiac function and key vascular beds for blood pressure control); T1–T6 levels as “mid” injuries (potential loss of autonomic control of key vascular beds for blood pressure control, but minimal impairment to cardiac function); and SCI levels below T6 as “low” injuries (largely intact cardiovascular autonomic function).

## Lipoprotein and metabolic measures

Fasting blood samples were taken to determine the lipoprotein profile (high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C] and total cholesterol [TC]), as well as the fasting blood glucose and glycated haemoglobin levels (HbA1C). Participants were considered to have diabetes mellitus if their HbA1C levels were  $\geq 48 \text{ mmol} \cdot \text{mol}^{-1}$  or they were taking a medication associated with the treatment of diabetes (e.g. metformin or insulin). Standardised laboratory techniques were used.

## Cardiovascular autonomic function

We evaluated the integrity of cardiovascular autonomic function from the peak HR response ( $\text{HR}_{\text{peak}}$ ) to graded maximal exercise testing [13]. We also determined resting blood pressure, which is heavily influenced by the integrity of cardiovascular autonomic pathways after SCI. Systolic (SAP) and diastolic (DAP) arterial pressures were recorded using a digital sphygmomanometer while participants were seated in their wheelchair. We determined the prevalence of hypotension using World Health Organization (WHO) criteria: for men,  $\text{SAP} < 110 \text{ mmHg}$ ; for women,  $\text{SAP} < 100 \text{ mmHg}$ .  $\text{HR}_{\text{peak}}$  (Polar Electro, Kempele, Finland) and peak oxygen uptake ( $\text{VO}_{2\text{peak}}$ , Oxycon Delta) responses to exercise were determined while participants performed a standardised graded peak wheelchair exercise test using a manual wheelchair on a treadmill [26]. The test was preceded by 5 min of seated rest. Participants then began manually wheeling at a speed of 2 km/h for those with tetraplegia and 4 km/h for those with paraplegia (3 km/h was used if the other options were too slow or too fast for the individual). The treadmill incline was increased by  $0.36^\circ$  every minute until the test was terminated because of exhaustion or inability to keep pace with the speed. The  $\text{HR}_{\text{peak}}$  was determined as the highest 5 s average HR during the test. Chronotropic incompetence (CI) was defined as a  $\text{HR}_{\text{peak}} < 125$  beats per minute (based on peak responses observed previously in those with high-level SCI and associated CI) [9].

## Cardiovascular disease risk

We used the FRS to calculate both the 10-year [29] and 30-year [30] CVD risk. This score utilises the following risk factors: sex; age; smoking status; diabetes; SAP; anti-hypertensive treatment; HDL-C; and TC. However, because SCI can impair blood pressure regulation (particularly with lesions above T6) such that a lower SAP in a SCI population may not be associated with a reduced overall CVD risk in the same way as seen in able-bodied individuals, a neutral SAP of 120 mmHg was used when calculating the risk score. A risk score of 10% is considered “intermediate risk” and this was the cut-point used for classifying “at-risk” individuals [29].

## Statistical analyses

Statistical analyses were performed using SigmaPlot statistical software (version 13; Systat Software Inc., San Jose, CA) and R (version 3.5.1, 2015). Continuous data were tested for normality using the Shapiro–Wilk test and parametric or nonparametric statistics used accordingly. Correlations were performed using Spearman’s rank-order tests

(nonparametric data) or Pearson's product moment analyses (parametric data) to examine the relationships between anthropometric measures, individual risk factors and 10-year and 30-year FRS. Numeric variables included: age (years); DOI (years); WC (cm); BMI ( $\text{kg} \cdot \text{m}^{-2}$ ); WHtR ( $\text{cm} \cdot \text{m}^{-1}$ ); HbA1C ( $\text{mmol} \cdot \text{mol}^{-1}$ ); HDL-C ( $\text{mmol} \cdot \text{L}^{-1}$ ); TC ( $\text{mmol} \cdot \text{L}^{-1}$ ) and  $\text{VO}_{2\text{peak}}$  ( $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Categorical variables included: sex (1 = male, 2 = female); presence of diabetes (0 = non-diabetic, 1 = diabetic); smoking status (0 = non-smoker, 1 = smoker; defined as currently smoking, having smoked within the last 5 years, or having smoked >20 pack years in the last 15 years [31, 32]).

Several variables were incorporated in the analyses as both numeric and categorical parameters: FRS (categorical: "at-risk"  $\text{FRS} \geq 10\% = 1$ ; not "at-risk"  $\text{FRS} < 10\% = 0$ ; numeric: risk score %); LOI (categorical: "high" = 1, "mid" = 2, or "low" = 3; ordinal, handled as numeric: C1 = 1, C2 = 2 etc); AIS (categorical: complete (A) = 1, incomplete (B–D) = 2; ordinal, handled as numeric: A = 1, B = 2, C = 3, D = 4);  $\text{HR}_{\text{peak}}$  (categorical: CI present ( $\text{HR}_{\text{peak}} < 125 \text{ bpm}$ ) = 1, CI absent ( $\text{HR}_{\text{peak}} \geq 125 \text{ bpm}$ ) = 0; numeric:  $\text{HR}_{\text{peak}}$  bpm); SAP (categorical: normal (110–140 mmHg) = 0, abnormal ( $< 110 \text{ mmHg}$  or  $> 140 \text{ mmHg}$ ) = 1; numeric: SAP mmHg). This approach was taken because we felt it might be preferable clinically to use categorical values for risk assessment, but we wanted to validate that information contained in the linear analyses was not being lost with this approach. Forced linear regression models, and Akaike information criterion (AIC) model-averaging were used to assess the impact of each variable on the FRS. We did not include potential predictors in the model that were incorporated in the generation of the FRS score. Receiver operator characteristic (ROC) curves were produced, and the area under the curve (AUC) calculated. Cut-points were determined using the Euclidean, Youden, and Product indices, derived from the sensitivity and specificity values generated from ROC analysis [33, 34]. Agreement between at least two indices was necessary for a cut-point recommendation [33]. Unbiased recursive partitioning (URP) was employed as an additional method to confirm variables of interest and their cut-points. URP identifies homogenous subgroups from an initial heterogeneous population, creating conditional inference trees [35]. Where sample sizes permitted, separate analyses were conducted for male and female participants. Sex differences were determined using unpaired student *t* tests (parametric data) or Mann–Whitney *U* tests (nonparametric data) and chi-squared analyses for proportions. The level of significance was set at  $p < 0.05$ . Continuous data are reported as mean  $\pm$  standard error unless stated otherwise; categorical variables are reported as percentages.

## Results

### Participants

A total of 282 individuals participated in the study. We were specifically interested in the effects of traumatic SCI, so data from 257 individuals (61 females) aged  $47 \pm 8$  (SD) years with chronic ( $24 \pm 9$  (SD) years) traumatic SCI were included in the analyses. Participant characteristics are shown in Table 1. For various reasons not all data were collected in all participants; sample sizes for each measure are provided in Table 1. Most lesions were cervical (45%) or thoracic (50%); 71% were motor/sensory complete and 79% had lesions that could affect cardiovascular autonomic control (at or above T6). For the cohort as a whole, 87 individuals (38%: 82 male and 5 female) were considered "at-risk" of CVD using the 10-year FRS, and 176 individuals (77%: 149 male and 27 female) were "at-risk" of CVD using the 30-year FRS. Male sex was associated with higher 10-year and 30-year FRS, and a higher prevalence of resting hypotension and diabetes. Males also had significantly higher WC, HbA1C and lower HDL-C. Males had higher  $\text{VO}_{2\text{peak}}$ , but not higher  $\text{HR}_{\text{peak}}$ , than females (Table 1). Older individuals had higher 10-year ( $r = 0.70$ ;  $p < 0.001$ ;  $n = 228$ ) and 30-year ( $r = 0.64$ ;  $p < 0.001$ ;  $n = 228$ ) FRS.

### Anthropometric measures and FRS

All three anthropometric measures (WC, WHtR and BMI) were positively correlated with both the 10-year and 30-year FRS for all participants combined, as well as for the male cohort (Table 2). Correlations were not statistically significant in females, in whom the sample size was much smaller. For the group as a whole, WC had the numerically highest correlation with both 10-year and 30-year CVD risk.

ROC curves were generated for all three anthropometric measures and both the 10-year and 30-year FRS (Fig. 1). The AUC for WC was significantly greater than both BMI ( $p = 0.002$ ) and WHtR ( $p = 0.04$ ) for the 30-year FRS, and greater than WHtR ( $p = 0.02$ ) for the 10-year FRS. Using the sensitivity and specificity values derived from the ROC analysis, optimal WC cut-points for identification of "at-risk" individuals were 97 cm and 94 cm for males, for the 10-year and 30-year FRS respectively (Supplementary Table 2). Note that only 5 women were "at-risk" for the 10-year FRS, and only 27 women "at-risk" for the 30-year FRS, and accordingly the determination of the cut-point criteria, particularly for 10-year risk, in females is not considered reliable. The cut-point for the 30-year risk was 80 cm for females, but should be considered with caution due to the low sample size.



**Table 1** Participant characteristics.

| Characteristic   | All         | <i>n</i> | Male              | <i>n</i>   | Female            | <i>n</i>  | <i>p</i> value   |
|--|-------------|----------|-------------------|------------|-------------------|-----------|------------------|
| Age (years)  | 47 ± 8      | 257      | 47 ± 9            | 196        | 47 ± 9            | 61        | 0.98             |
| Duration of injury (years)                                       | 24 ± 9      | 257      | 24 ± 9            | 196        | 23 ± 9            | 61        | 0.86             |
| Level of injury (%)  |             |          |                   |            |                   |           |                  |
| Cervical   | 45          | 114      | 47                | 93         | 34                | 21        | 0.07             |
| Thoracic   | 50          | 128      | 47                | 92         | 59                | 36        | 0.10             |
| Lumbar   | 5           | 14       | 6                 | 11         | 5                 | 3         | 0.77             |
| Sacral   | 0           | 0        |                   |            |                   |           |                  |
| Motor/sensory completeness of injury (%)                         |             |          |                   |            |                   |           |                  |
| Complete   | 71          | 183      | 70                | 138        | 75                | 45        | 0.45             |
| Incomplete   | 29          | 73       | 30                | 58         | 25                | 15        | 0.45             |
| Stratification by autonomic impairment (%)                       |             |          |                   |            |                   |           |                  |
| High (C1–C8)   | 45          | 114      | 47                | 93         | 34                | 21        | 0.07             |
| Mid (T1–T6)  | 34          | 88       | 32                | 63         | 41                | 25        | 0.20             |
| Low (Below T6)   | 21          | 54       | 20                | 40         | 23                | 14        | 0.61             |
| BMI (kg · m <sup>-2</sup> )                                      | 25 ± 5      | 254      | 26 ± 5            | 193        | 25 ± 5            | 61        | 0.21             |
| WC (cm)  | 97 ± 15     | 239      | <b>100 ± 14</b>   | <b>184</b> | <b>89 ± 14</b>    | <b>55</b> | <b>&lt;0.001</b> |
| WHtR (cm · m <sup>-1</sup> )                                     | 0.54 ± 0.08 | 238      | 0.55 ± 0.08       | 183        | 0.53 ± 0.09       | 55        | 0.14             |
| HbA1C (mmol · mol <sup>-1</sup> )                                | 36 ± 7      | 209      | <b>37 ± 8</b>     | <b>160</b> | <b>35 ± 4</b>     | <b>49</b> | <b>0.04</b>      |
| Diabetes (%)   | 12          | 25       | <b>15</b>         | <b>24</b>  | <b>2</b>          | <b>1</b>  | <b>0.01</b>      |
| Smoking (%)  | 35          | 89       | 35                | 69         | 33                | 20        | 0.77             |
| HDL-C (mmol · L <sup>-1</sup> )                                  | 1.2 ± 0.36  | 228      | <b>1.1 ± 0.28</b> | <b>172</b> | <b>1.5 ± 0.45</b> | <b>56</b> | <b>&lt;0.001</b> |
| TC (mmol · L <sup>-1</sup> )                                     | 4.9 ± 1     | 228      | 4.8 ± 1           | 172        | 5.1 ± 1           | 56        | 0.06             |
| SAP (mmHg)   | 126 ± 26    | 253      | 125 ± 26          | 192        | 126 ± 25          | 61        | 0.78             |
| HR <sub>peak</sub> (bpm)   | 147 ± 29    | 156      | 145 ± 30          | 118        | 152 ± 26          | 38        | 0.24             |
| VO <sub>2peak</sub> (ml · min <sup>-1</sup> · kg <sup>-1</sup> ) | 17.1 ± 6.1  | 160      | <b>17.8 ± 6.2</b> | <b>118</b> | <b>15.2 ± 5.4</b> | <b>42</b> | <b>0.017</b>     |
| Hypotension (%)  | 26          | 69       | <b>30</b>         | <b>57</b>  | <b>13</b>         | <b>8</b>  | <b>0.01</b>      |
| CI (%)   | 23          | 36       | 25                | 29         | 47                | 7         | 0.43             |
| 10-year FRS (%)  | 10 ± 8      | 227      | <b>12 ± 8</b>     | <b>172</b> | <b>5 ± 4</b>      | <b>55</b> | <b>&lt;0.001</b> |
| 10-year increased FRS (%)  | 38          | 87       | <b>48</b>         | <b>82</b>  | <b>9</b>          | <b>5</b>  | <b>&lt;0.001</b> |
| 30-year FRS (%)  | 23 ± 16     | 228      | <b>27 ± 16</b>    | <b>172</b> | <b>14 ± 10</b>    | <b>56</b> | <b>&lt;0.001</b> |
| 30-year increased FRS (%)  | 77          | 176      | <b>87</b>         | <b>149</b> | <b>50</b>         | <b>27</b> | <b>&lt;0.001</b> |

Data are presented as mean ± standard deviation or percentages. Note that not all measures were obtained in all participants. Bold text denotes significant differences ( $p < 0.05$ ) between males and females, with significance indicated in the last column ( $p$  value).

*BMI* body mass index, *WC* waist circumference, *WHtR* waist-height ratio, *HbA1C* glycated haemoglobin, *HDL-C* high-density lipoprotein cholesterol, *TC* total cholesterol, *SAP* systolic arterial pressure, *HR<sub>peak</sub>* maximum heart rate at peak aerobic capacity, *VO<sub>2peak</sub>* peak oxygen uptake during maximal exercise, *CI* chronotropic incompetence, *FRS* Framingham risk score, *n* sample size.

## Anthropometric measures and CVD risk factors

Correlations between anthropometric measures and traditional CVD risk factors are shown in Table 3. All three anthropometric measures were positively correlated with age, and the presence of diabetes, and negatively correlated with HDL-C. WC was the only anthropometric measure significantly correlated with sex, with males having a larger WC. BMI was also positively correlated with SAP, HbA1C and TC.

## Impact of injury characteristics on CVD risk factors and FRS

Correlations between injury characteristics, traditional CVD risk factors, and FRS scores are shown in Table 4. Longer duration injuries were associated with higher SAP, greater adiposity (WC, WHtR), an increased 10-year and 30-year FRS, and older age ( $r = 0.851$ ;  $p < 0.0001$ ;  $n = 257$ ).

Higher level injuries were associated with greater impairments in cardiovascular autonomic function (lower

**Table 2** Correlations between markers of obesity and 10-year and 30-year FRS.

|  | 10-year FRS (%)  |  |  | 30-year FRS (%)  |  |  |
|--|--|--|--|--|--|--|
|  | All  | Male   | Female                                 | All  | Male   | Female                                 |
| WC (cm)                                  | <b><math>r = 0.406</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 210</math></b> | <b><math>r = 0.328</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 160</math></b> | $r = 0.247$<br>$p = 0.084$<br>$n = 50$ | <b><math>r = 0.415</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 210</math></b> | <b><math>r = 0.355</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 160</math></b> | $r = 0.245$<br>$p = 0.087$<br>$n = 50$ |
| BMI ( $\text{kg} \cdot \text{m}^{-2}$ )  | <b><math>r = 0.340</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 226</math></b> | <b><math>r = 0.398</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 170</math></b> | $r = 0.077$<br>$p = 0.569$<br>$n = 56$ | <b><math>r = 0.367</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 226</math></b> | <b><math>r = 0.436</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 170</math></b> | $r = 0.105$<br>$p = 0.439$<br>$n = 56$ |
| WHtR ( $\text{cm} \cdot \text{m}^{-1}$ ) | <b><math>r = 0.351</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 209</math></b> | <b><math>r = 0.356</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 159</math></b> | $r = 0.234$<br>$p = 0.102$<br>$n = 50$ | <b><math>r = 0.368</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 209</math></b> | <b><math>r = 0.380</math></b><br><b><math>p &lt; 0.001</math></b><br><b><math>n = 159</math></b> | $r = 0.246$<br>$p = 0.085$<br>$n = 50$ |

Bold text indicates correlations that achieved statistical significance ( $p < 0.05$ ). Correlation coefficients ( $r$ ), significance levels ( $p$ ), and sample sizes ( $n$ ) are shown.

WC waist circumference, BMI body mass index, WHtR waist-height ratio, FRS numeric Framingham risk score.

HR<sub>peak</sub>), as well as a lower SAP and HDL-C. Those with higher LOI were also less likely to smoke and tended to have a higher WC ( $p = 0.056$ ). LOI was not significantly correlated with the 10-year or 30-year FRS.

Lower AIS scores (more complete lesions) were associated with higher HR<sub>peak</sub>, SAP, and prevalence of diabetes, and a lower LOI ( $r = -0.25$ ;  $p < 0.001$ ;  $n = 256$ ). The AIS score was not significantly correlated with the 10-year or 30-year FRS.

Impaired autonomic function (lower HR<sub>peak</sub>) was associated with lower SAP. Impaired HR<sub>peak</sub> and higher SAP were associated with increased 10-year and 30-year FRS. Impaired HR<sub>peak</sub> was associated with higher LOI and greater WC. Higher SAP was associated with lower LOI, longer DOI, higher TC and HDL-C, higher HbA1C, and higher BMI (Table 4).

We also examined whether fitness, inferred by VO<sub>2peak</sub>, was associated with FRS scores. There were no statistically significant correlations between VO<sub>2peak</sub> ( $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and either 10-year ( $r = -0.21$ ,  $p = 0.80$ ;  $n = 141$ ) or 30-year ( $r = -0.034$ ,  $p = 0.693$ ;  $n = 141$ ) FRS.

ROC analyses were performed for each injury characteristic and cut-points for an increased risk of CVD determined using the derived sensitivity and specificity (Supplementary Table 3). Individuals with a WC in excess of 95 cm, DOI > 23 years, HR<sub>peak</sub> < 145 bpm, or SAP > 128 mmHg had a higher 10-year FRS. Cut-point criteria for AIS and LOI indicate a threshold level for increased CVD risk at C8-T2, with AIS A completeness, but these were not statistically significant for either 10-year or 30-year FRS. The 30-year FRS was greater in those with a WC in excess of 94 cm, DOI > 20 years, HR<sub>peak</sub> < 154 bpm and SAP > 113 mmHg.

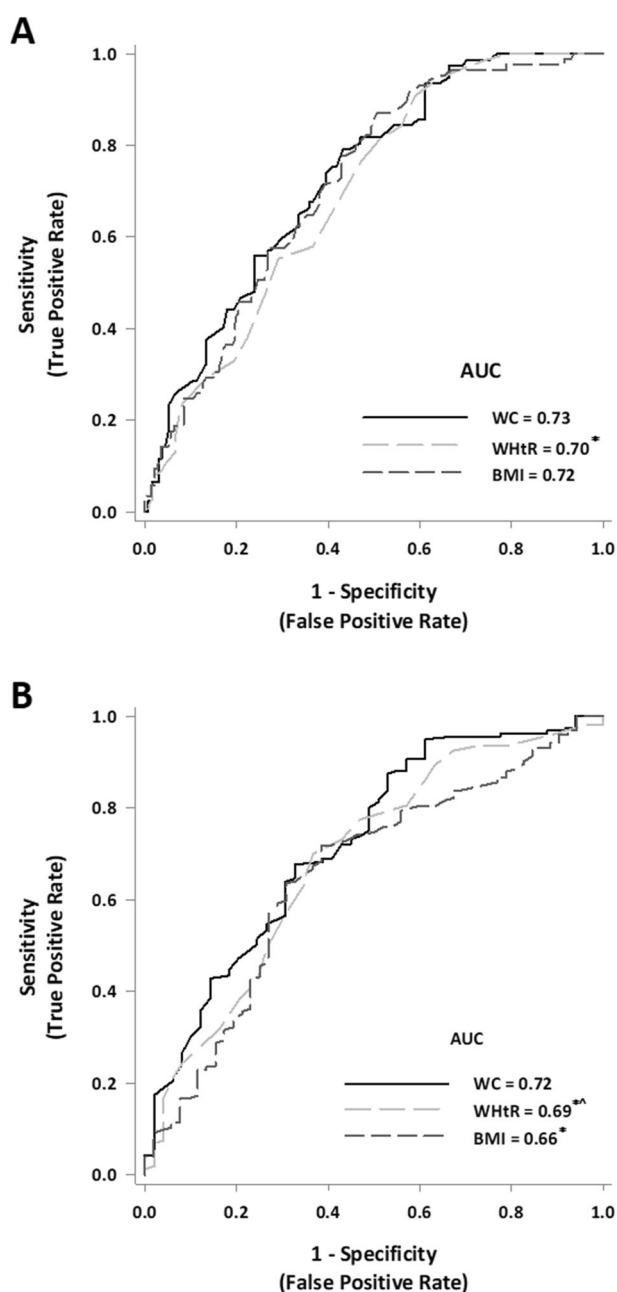
### Associations between CVD risk factors, FRS and obesity in SCI

We constructed a forced multiple linear regression model to determine the key predictors of the 10-year and 30-year

FRS (Table 5). We did not include parameters in the model that were already incorporated in the generation of the FRS score. Based on these analyses, the significant predictors of an adverse 10-year and 30-year FRS were a longer DOI, impaired autonomic function (lower HR<sub>peak</sub>) and higher SAP. There was a trend for a higher WC to be associated with adverse 10-year ( $p = 0.058$ ) and 30-year ( $p = 0.054$ ) FRS. LOI also tended to be associated with the 10-year FRS ( $p = 0.056$ ) and was significantly associated with the 30-year FRS ( $p = 0.031$ ). Aerobic capacity tended to be associated with the 10-year FRS ( $p = 0.068$ ) but not with the 30-year FRS ( $p = 0.141$ ).

We employed AIC model-averaging to determine variable importance in estimating 10-year and 30-year FRS. After running 271 models for 10-year FRS, and 296 models for 30-year FRS, a larger WC, longer DOI, and higher SAP had high variable importance (appearing in more than 80% of all models), while a lower HR<sub>peak</sub>, higher VO<sub>2peak</sub> and low LOI (cat) had moderate variable importance (appearing in 60–80% of all models) for estimating the 10-year FRS. All these variables had high variable importance for estimating the 30-year FRS (Fig. 2) with the exception of VO<sub>2peak</sub>, which was no longer an important predictor.

Figure 3 shows conditional inference trees for 10-year and 30-year CVD risk. URP was employed to both determine and confirm cut-points, and independently identify predictors of CVD risk. The identification of homogenous subgroups is based on DOI and WC (10-year CVD risk), and DOI, WC, and SAP (30-year CVD risk), confirming the predictive importance of these variables (variables that do not appear in the trees are not significant predictors). All variables are re-entered after each split, such that a given variable can appear multiple times in the tree. The final nodes at the bottom show the full distribution of CVD risk using box plots. Cut-points for DOI were similar to those determined through ROC analyses. Cut-points for WC based on URP depended on the DOI. For example, in



**Fig. 1** Receiver operator characteristic (ROC) curves showing the ability of markers of obesity to predict an adverse Framingham Risk Score. (A) Prediction of 10-year Framingham Risk Score. (B) Prediction of 30-year Framingham Risk Score. The area under the curve (AUC) for each metric is provided; a higher AUC signifies a greater ability to correctly classify at-risk individuals. \* $p < 0.05$  compared to WC, \*\* $p < 0.05$  compared to BMI. WC waist circumference, BMI body mass index, WHtR waist-to-height ratio.

individuals who had a longer DOI ( $>20$  years) the 10-year FRS was reduced if WC was  $<94$  cm. However, in those who had a shorter DOI ( $\leq 20$  years), and therefore an inherently lower CVD risk, further reduction was only seen where WC was  $<80$  cm.

## Discussion

The main findings of this study are that measures of obesity can be used to infer CVD risk following SCI, with WC being the strongest obesity-related predictor for CVD risk. Unlike BMI and WHtR, only WC was significantly associated with both DOI and impaired cardiac autonomic function ( $HR_{peak}$ ). This suggests that WC may provide additional information beyond obesity and other traditional cardiovascular risk factors, that may play a role in the earlier onset and faster progression of CVD following SCI [5], such as autonomic dysfunction and specific injury characteristics. This study suggests a WC cut-point for males for an increased 10-year CVD risk following SCI of 97 cm, which is lower than the cut-point for able-bodied males (102 cm) [36] and reflects the higher CVD risk in this population [5]. These results are similar to those reported by Ravensbergen et al. [25] in a small North American cohort of individuals with SCI. Due to a low number of females, and in particular a low number of females “at-risk” for CVD, a reliable cut-point for 10-year CVD risk in females with SCI could not be determined. Accordingly, at the present time we recommend use of the able-bodied cut-point of 88 cm [36] to stratify CVD risk in women with SCI, until risk profiles can be confirmed in a larger sample of women with SCI “at-risk” for CVD. We note, however, that this may be an overestimate of the optimal cut-point for women with SCI in light of the reduced cut-point for males with SCI, and the lower cut-point for the 30-year risk for females in this study of 80 cm.

Given that WC performed as well as, or better than, BMI and WHtR in terms of its ability to predict CVD risk, and its known relationship to visceral adipose tissue [22] and cardiometabolic risk [17], from a practicality standpoint we advocate for the routine use of WC as a screening tool for both individuals with SCI and their caregivers to consider to assess CVD risk and guide healthy weight management. In practical terms, when determining WC in individuals with SCI, measurements should be conducted in the supine position, at the narrowest part of the waist, and at the end of a normal expiration, with a stretch-resistant measuring tape. This is important to ensure reliable estimates of WC, and to avoid the potential confound of flaccid paralysis of the abdominal muscles on measurements of WC when performed in the seated position. Males with a WC  $>97$  cm, and females with a WC  $>88$  cm, should be considered at higher risk for CVD and advised regarding risk management strategies accordingly. While these cut-points are useful for identifying “at-risk” individuals, WC is a modifiable factor that can be used to reduce CVD risk whether or not the cut-point is attained. Based on this study, there is a reduction in the FRS of  $\sim 1\%$  for every 2–5 cm reduction in WC, with URP analyses showing up to 75% FRS



**Table 3** Correlations between markers of obesity and traditional CVD risk factors.

|                              | Sex  | Age (years)   | Smoking   | Diabetes  | SAP<br>(mmHg)   | HbA1C<br>(mmol · mol <sup>-1</sup> )  | HDL-C<br>(mmol · L <sup>-1</sup> )   | TC<br>(mmol · L <sup>-1</sup> )   |
|------------------------------|--|---|---|---|---|---|--|---|
| WC (cm)                      | <i>r</i> = <b>-0.283</b><br><i>p</i> < <b>0.001</b><br><i>n</i> = <b>239</b> | <i>r</i> = <b>0.194</b><br><i>p</i> = <b>0.003</b><br><i>n</i> = <b>239</b> | <i>r</i> = -0.018<br><i>p</i> = 0.778<br><i>n</i> = 238 | <i>r</i> = <b>0.281</b><br><i>p</i> < <b>0.001</b><br><i>n</i> = <b>211</b> | <i>r</i> = 0.091<br><i>p</i> = 0.163<br><i>n</i> = 236                      | <i>r</i> = 0.136<br><i>p</i> = 0.061<br><i>n</i> = 192                      | <i>r</i> = <b>-0.428</b><br><i>p</i> < <b>0.001</b><br><i>n</i> = <b>210</b> | <i>r</i> = 0.037<br><i>p</i> = 0.591<br><i>n</i> = 210                      |
| BMI (kg · m <sup>2</sup> )   | <i>r</i> = -0.086<br><i>p</i> = 0.169<br><i>n</i> = 254                      | <i>r</i> = <b>0.128</b><br><i>p</i> = <b>0.042</b><br><i>n</i> = <b>254</b> | <i>r</i> = 0.060<br><i>p</i> = 0.345<br><i>n</i> = 253  | <i>r</i> = <b>0.223</b><br><i>p</i> < <b>0.001</b><br><i>n</i> = <b>227</b> | <i>r</i> = <b>0.133</b><br><i>p</i> = <b>0.036</b><br><i>n</i> = <b>250</b> | <i>r</i> = <b>0.165</b><br><i>p</i> = <b>0.018</b><br><i>n</i> = <b>207</b> | <i>r</i> = <b>-0.370</b><br><i>p</i> < <b>0.001</b><br><i>n</i> = <b>226</b> | <i>r</i> = <b>0.160</b><br><i>p</i> = <b>0.017</b><br><i>n</i> = <b>226</b> |
| WHtR (cm · m <sup>-1</sup> ) | <i>r</i> = -0.092<br><i>p</i> = 0.159<br><i>n</i> = 238                      | <i>r</i> = <b>0.219</b><br><i>p</i> < <b>0.001</b><br><i>n</i> = <b>238</b> | <i>r</i> = -0.001<br><i>p</i> = 0.985<br><i>n</i> = 237 | <i>r</i> = <b>0.240</b><br><i>p</i> < <b>0.001</b><br><i>n</i> = <b>210</b> | <i>r</i> = 0.071<br><i>p</i> = 0.279<br><i>n</i> = 235                      | <i>r</i> = 0.103<br><i>p</i> = 0.155<br><i>n</i> = 191                      | <i>r</i> = <b>-0.407</b><br><i>p</i> < <b>0.001</b><br><i>n</i> = <b>209</b> | <i>r</i> = 0.067<br><i>p</i> = 0.335<br><i>n</i> = 209                      |

Bold text indicates correlations that achieved statistical significance ( $p < 0.05$ ). Correlation coefficients ( $r$ ), significance levels ( $p$ ) and sample sizes ( $n$ ) are shown. Categorical data: sex (1 = male, 2 = female); presence of diabetes (0 = non-diabetic, 1 = diabetic); smoking status (0 = non-smoker, 1 = smoker).

WC waist circumference, BMI body mass index, WHtR waist-to-height ratio, SAP systolic arterial pressure, HbA1C glycated haemoglobin, HDL-C high density lipoprotein cholesterol, TC total cholesterol.

reduction between subgroups. Previous studies have identified a 20–25% reduction in FRS as biologically meaningful [37, 38]. Individuals with an adverse risk profile (considering both traditional and injury-related risk factors) should be targeted for aggressive management of risk using lifestyle modification and/or pharmacologic therapy.

A secondary aim of this study was to better understand the CVD risk profile for individuals with SCI, including consideration of unique risk parameters such as injury characteristics and autonomic function, and their relationship with CVD risk. Traditional CVD risk factors were also considered important variables, and known traditional risk factors in the able-bodied (smoking, presence of diabetes, adverse lipid profiles etc.) were also pertinent risk factors for individuals with SCI. Accordingly, smoking cessation and careful management of diabetes and lipid profiles remain important considerations to reduce CVD risk following SCI, particularly because individuals with SCI are at higher risk for diabetes and metabolic syndrome [39, 40], and the proportion of individuals with diabetes and who were smokers in this SCI cohort was considerably higher than in a matched able-bodied cohort [41, 42]. As in the able-bodied [43], males were at higher risk of CVD than females, and CVD risk increased with advancing age following SCI.

We found that a longer DOI (particularly if in excess of ~20 years) was associated with increasing CVD risk. DOI is a covariate with age, so at the present time it is unclear whether the relationships between DOI and CVD risk reflect an indirect effect of advancing age on CVD risk and/or a direct impact of a longer time living with SCI, particularly because our recruitment criteria excluded individuals with recent injuries. While DOI was identified as a key variable in terms of cardiovascular risk, it is, obviously, not modifiable and so we focussed much of our attention on WC as a modifiable parameter.

The relationship between LOI and CVD risk is complex. There is no independent correlation between LOI and FRS. However, we identified a threshold for CVD risk whereby those with cervical and high-thoracic lesions tended to be at greater risk based on ROC analyses. When data were adjusted for other factors using regression and AIC analyses we found an increased risk of CVD in those with low-level lesions. Motor/sensory completeness of injury was also not an important independent predictor of CVD risk; however, using ROC analyses we identified a threshold for CVD risk for those with AIS A injuries. Higher level motor/sensory complete injuries are associated with greater decrements in mobility and increased sedentary time, which are known to increase CVD risk [44]. There are also reports that nutritional status is further impaired in those with high-level motor/sensory complete lesions [16], and this might also have a negative impact on CVD risk. Indeed, those with high-level lesions tended to have adverse HDL-C profiles. Conversely, those with low-level lesions were more likely to smoke and have high blood pressure, all factors that might adversely impact risk, despite their preserved cardiovascular autonomic function.

The severity of impairment to cardiovascular autonomic function (considered in this study from the ability to increase HR during exercise) was an important independent factor in predicting the increased CVD burden following SCI. One benefit of this measure is that it does not necessarily require a laboratory-based exercise test for evaluation. If an individual is able to undertake a bout of moderate-vigorous aerobic exercise as part of their activities of daily living, and HR increases to ~125–140 bpm, the assumption can be made that there is at least some residual sympathetic control of the cardiovascular system, and a decreased risk of CVD. For individuals who complete moderate-vigorous activity in whom HR does not exceed this threshold, the

**Table 4** Correlations between injury characteristics, traditional CVD risk factors, and 10-year and 30-year FRS.

|                          | Smoking                                  | Diabetes                                 | HR <sub>peak</sub> (bpm)                 | SAP (mmHg)                               | HbA1C (mmol · mol <sup>-1</sup> )        | HDL-C (mmol · L <sup>-1</sup> )         | TC (mmol · L <sup>-1</sup> )             | WC (cm)                                  | BMI (kg · m <sup>-2</sup> )              | WHR (cm · m <sup>-1</sup> )              | 10-year FRS (%)                          | 30-year FRS (%)                          |
|--------------------------|--|--|--|--|--|---|--|--|--|--|--|--|
| DOI (months)             | $r = -0.083$<br>$p = 0.183$<br>$n = 256$ | $r = 0.068$<br>$p = 0.304$<br>$n = 229$  | $r = -0.142$<br>$p = 0.077$<br>$n = 156$ | $r = 0.244$<br>$p < 0.001$<br>$n = 253$  | $r = 0.124$<br>$p = 0.075$<br>$n = 209$  | $r = 0.037$<br>$p = 0.580$<br>$n = 228$ | $r = 0.070$<br>$p = 0.290$<br>$n = 228$  | $r = 0.195$<br>$p = 0.002$<br>$n = 239$  | $r = 0.099$<br>$p = 0.116$<br>$n = 254$  | $r = 0.221$<br>$p < 0.001$<br>$n = 238$  | $r = 0.548$<br>$p < 0.001$<br>$n = 228$  | $r = 0.493$<br>$p < 0.001$<br>$n = 228$  |
| LOI (...)                | $r = 0.126$<br>$p = 0.044$<br>$n = 255$  | $r = -0.015$<br>$p = 0.820$<br>$n = 229$ | $r = 0.619$<br>$p < 0.001$<br>$n = 156$  | $r = 0.443$<br>$p < 0.001$<br>$n = 253$  | $r = 0.116$<br>$p = 0.094$<br>$n = 209$  | $r = 0.144$<br>$p = 0.029$<br>$n = 228$ | $r = 0.075$<br>$p = 0.257$<br>$n = 228$  | $r = -0.124$<br>$p = 0.056$<br>$n = 238$ | $r = 0.024$<br>$p = 0.701$<br>$n = 253$  | $r = -0.099$<br>$p = 0.128$<br>$n = 237$ | $r = 0.023$<br>$p = 0.735$<br>$n = 227$  | $r = 0.027$<br>$p = 0.691$<br>$n = 228$  |
| AIS (...)                | $r = -0.112$<br>$p = 0.074$<br>$n = 255$ | $r = -0.135$<br>$p = 0.042$<br>$n = 229$ | $r = -0.252$<br>$p < 0.001$<br>$n = 156$ | $r = -0.150$<br>$p = 0.017$<br>$n = 252$ | $r = -0.069$<br>$p = 0.324$<br>$n = 209$ | $r = 0.030$<br>$p = 0.652$<br>$n = 228$ | $r = 0.113$<br>$p = 0.089$<br>$n = 228$  | $r = -0.012$<br>$p = 0.859$<br>$n = 238$ | $r = -0.009$<br>$p = 0.887$<br>$n = 253$ | $r = -0.041$<br>$p = 0.528$<br>$n = 237$ | $r = 0.035$<br>$p = 0.597$<br>$n = 228$  | $r = 0.026$<br>$p = 0.697$<br>$n = 228$  |
| HR <sub>peak</sub> (bpm) | $r = -0.004$<br>$p = 0.966$<br>$n = 155$ | $r = -0.099$<br>$p = 0.247$<br>$n = 138$ | –  | $r = 0.358$<br>$p < 0.001$<br>$n = 155$  | $r = -0.014$<br>$p = 0.884$<br>$n = 124$ | $r = 0.090$<br>$p = 0.295$<br>$n = 138$ | $r = -0.025$<br>$p = 0.768$<br>$n = 138$ | $r = -0.168$<br>$p = 0.042$<br>$n = 147$ | $r = -0.030$<br>$p = 0.707$<br>$n = 155$ | $r = -0.121$<br>$p = 0.144$<br>$n = 146$ | $r = -0.201$<br>$p = 0.018$<br>$n = 138$ | $r = -0.186$<br>$p = 0.029$<br>$n = 138$ |
| SAP (mmHg)               | $r = 0.081$<br>$p = 0.202$<br>$n = 252$  | $r = 0.086$<br>$p = 0.198$<br>$n = 225$  | $r = 0.358$<br>$p < 0.001$<br>$n = 155$  | –  | $r = 0.279$<br>$p < 0.001$<br>$n = 206$  | $r = 0.162$<br>$p = 0.015$<br>$n = 224$ | $r = 0.160$<br>$p = 0.016$<br>$n = 224$  | $r = 0.091$<br>$p = 0.163$<br>$n = 236$  | $r = 0.133$<br>$p = 0.036$<br>$n = 250$  | $r = 0.071$<br>$p = 0.279$<br>$n = 235$  | $r = 0.293$<br>$p < 0.001$<br>$n = 224$  | $r = 0.282$<br>$p < 0.001$<br>$n = 224$  |

Bold text indicates correlations that achieved statistical significance ( $p < 0.05$ ). Correlation coefficients (r), significance levels (p) and sample sizes (n) are shown. Categorical data: presence of diabetes (0 = non-diabetic, 1 = diabetic); smoking status (0 = non-smoker, 1 = smoker).

DOI duration of injury, LOI numeric level of injury, AIS ordinal (considered as numeric) AIS impairment scale (A = 1, B = 2, C = 3, D = 4), HR<sub>peak</sub> maximum heart rate at peak aerobic capacity, SAP systolic arterial pressure, HbA1C glycated haemoglobin, HDL-C high density lipoprotein cholesterol, TC total cholesterol, WC waist circumference, BMI body mass index, WHR waist-height ratio, FRS numeric Framingham risk score.

**Table 5** Regression model outcomes for multivariate regression between injury characteristics, anthropometric variables and aerobic capacity and 10-year and 30-year FRS.

|  | 10-year FRS ( $n = 119$ ), $r = 0.604$ , $p < 0.001$ |                         |                  | 30-year FRS ( $n = 119$ ), $r = 0.599$ , $p < 0.001$ |                         |              |
|--|--|-------------------------|------------------|--|-------------------------|--------------|
|  | $\beta$ (SE)   | 95% confidence interval | $p$              | $\beta$ (SE)   | 95% confidence interval | $p$          |
| Constant                                 | -10.7 (7.6)  | 4.35 to -25.8           | 0.161            | -16.3 (15.8)   | 14.9 to -47.5           | 0.303        |
| WC (cm)                                  | 0.21 (0.11)  | 0.43 to -0.01           | 0.058            | 0.45 (0.23)  | 0.91 to -0.01           | 0.054        |
| BMI ( $\text{kg} \cdot \text{m}^2$ )     | 0.25 (0.30)  | 0.85 to -0.35           | 0.410            | 0.63 (0.63)  | 1.88 to -0.62           | 0.321        |
| WHtR ( $\text{cm} \cdot \text{m}^{-1}$ ) | -27.6 (25.1)   | 22.1 to -77.3           | 0.274            | -54.5 (52)   | 48.5 to -158            | 0.297        |
| DOI (months)                             | <b>0.26 (0.07)</b>                                   | <b>0.40 to 0.12</b>     | <b>&lt;0.001</b> | <b>0.40 (0.15)</b>                                   | <b>0.70 to 0.10</b>     | <b>0.010</b> |
| AIS                                      | 0.50 (0.62)  | 1.73 to -0.73           | 0.425            | 0.62 (1.28)  | 3.16 to -1.92           | 0.631        |
| LOI                                      | 1.89 (0.98)  | 3.83 to -0.05           | 0.056            | <b>4.42 (2.02)</b>                                   | <b>8.42 to 0.42</b>     | <b>0.031</b> |
| HR <sub>peak</sub> (bpm)                 | <b>-0.10 (0.04)</b>                                  | <b>-0.02 to -0.18</b>   | <b>0.006</b>     | <b>-0.24 (0.08)</b>                                  | <b>-0.08 to -0.40</b>   | <b>0.002</b> |
| CI                                       | -1.23 (2.12)   | 2.97 to -5.43           | 0.561            | -3.84 (4.38)   | 4.84 to -12.5           | 0.383        |
| SAP (mmHg)                               | <b>0.07 (0.03)</b>                                   | <b>0.13 to 0.01</b>     | <b>0.025</b>     | <b>0.16 (0.06)</b>                                   | <b>0.29 to 0.04</b>     | <b>0.016</b> |
| VO <sub>2peak</sub> (ml.min.kg)          | 0.21 (0.11)  | 0.43 to -0.01           | 0.068            | 0.35 (0.23)  | 0.81 to -0.11           | 0.141        |

Bold text indicates variables that were statistically significant contributors to the FRS. Sample sizes ( $n$ ), beta coefficients ( $\beta$ ), standard errors (SE), and significance levels ( $p$ ) are shown.

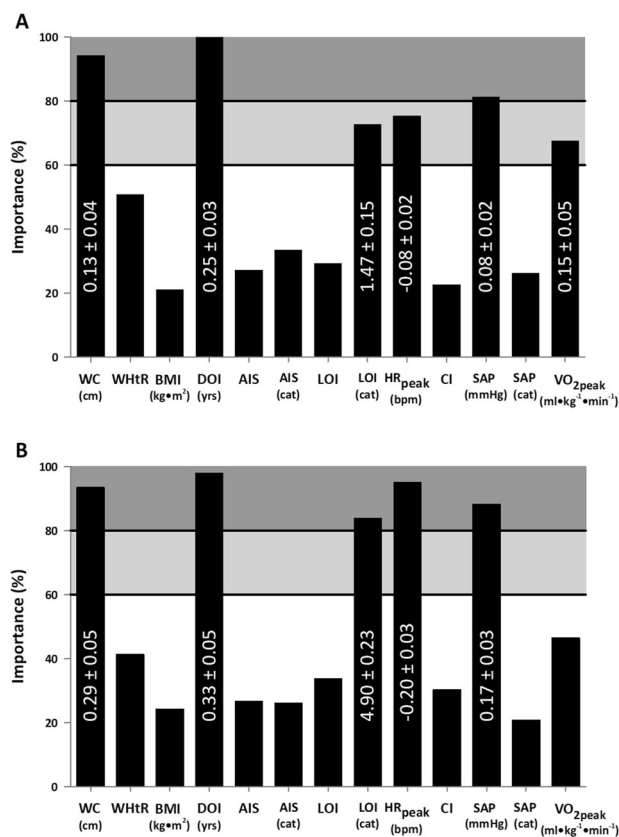
WC waist circumference, BMI body mass index, WHtR waist-to-height ratio, DOI duration of injury, AIS ordinal (considered as numeric) ASIA impairment scale (A = 1, B = 2, C = 3, D = 4), LOI level of injury categorised as high (1, C1–C8), mid (2, T1–T6), low (3, below T6), HR<sub>peak</sub> maximum heart rate at peak aerobic capacity, CI chronotropic incompetence categorised as present (1) or absent (0), SAP systolic arterial pressure incorporated as a linear variable, VO<sub>2peak</sub> peak oxygen uptake during maximal exercise, FRS numeric Framingham risk score.

CVD risk can be presumed to be high, and aggressive management of risk factors should be considered. One question that remains unanswered is whether the increased CVD risk associated with impaired HR regulation is a direct effect of the loss of descending control of the cardiovascular system, or an indirect effect of other factors known to increase mortality that would present as a consequence of the cardiovascular autonomic impairment, such as orthostatic hypotension [45, 46], AD [47], arrhythmias [11], and other vascular abnormalities [48].

The contribution of hypertension to CVD risk is typically incorporated within the FRS; however, it is unclear if the typical association between hypertension and CVD risk is present following SCI, as SCI is associated with altered cardiovascular reflex control of blood pressure [49]. Resting hypotension may present following injury above T6, as descending sympathetic pathways are compromised, and blood pressure regulation is impaired. In the able-bodied, lower SAP is protective against CVD risk [29]; however, in those with SCI, hypotension is strongly associated with susceptibility to AD [46]. These large blood pressure swings may contribute to impairments in cerebrovascular health and increased CVD mortality [50] and as such, resting hypotension may not necessarily be protective of CVD risk after SCI. In addition, accurate representation of resting blood pressure is difficult in individuals with SCI. Although we took care to minimise the risk of concurrent AD during blood pressure measurements, it is likely that some participants were experiencing AD, as reflected by some significantly elevated SAP (>150 mmHg) recordings in individuals with lesions above T6 ( $n = 33$ ).

Conversely, because we measured blood pressure in the seated position, and because of the high incidence of OH in individuals with SCI, we may also have exacerbated hypotensive recordings in susceptible individuals. These challenges with appropriate blood pressure determination in individuals with SCI may unpredictably influence risk calculations that utilise blood pressure metrics. Accordingly, we used a neutral blood pressure in the determination of the FRS. However, when we repeated our analyses using the recorded SAP rather than a neutral value, our results were essentially unchanged. Despite these nuances in the interpretation of blood pressure data in individuals with SCI, we did observe significant relationships between blood pressure abnormalities and FRS. When incorporated as a linear scale, there was an ~1% increase in FRS for every 10 mmHg increase in SAP. Whether this represents the known association between hypertension and CVD risk seen in the able-bodied [4], or reflects an association between AD and CVD risk [10, 48], or a combination of the two, cannot be determined from this study.

It is often assumed that individuals with SCI have a high risk for CVD because of the tendency to a more sedentary lifestyle secondary to associated paralysis and use of a wheelchair for mobility [18, 20]. While this may be at least partly true, in this study low VO<sub>2peak</sub> was not independently correlated with increased 10-year or 30-year FRS, suggesting other factors play at least an equally important role in determining CVD risk profiles. In fact, there was a trend for higher VO<sub>2peak</sub> to be associated with increased 10-year FRS (but not 30-year FRS) based on the regression data and



**Fig. 2 Akaike Information Criterion model-averaged importance of predictors of CVD risk.** WC, DOI, and SAP (considered as numeric) were highly important predictors, with HR<sub>peak</sub>, LOI (cat) and VO<sub>2peak</sub> being moderately important predictors of increased CVD risk for the 10-year FRS (A). WC, DOI, SAP, HR<sub>peak</sub>, and LOI (cat) were highly important predictors for the 30-year FRS (B). The horizontal bars represent high (appears in >80% of models) and moderate (appears in 60–80% of models) variable importance. Beta coefficients ± standard errors are provided for parameters with moderate-high variable importance. WC waist circumference, WHtR waist-to-height ratio, BMI body mass index, DOI duration of injury, AIS ordinal (considered as numeric) ASIA impairment scale (A = 1, B = 2, C = 3, D = 4), AIS (cat) ASIA impairment scale categorised as complete (1, AIS A) or incomplete injury (0, AIS B–D), LOI numeric level of injury, LOI (cat) level of injury categorised as a high (1, C1–C8), mid (2, T1–T6), or low (3, below T6) injury, HR<sub>peak</sub> maximum heart rate at peak aerobic capacity, CI chronotropic incompetence categorised as present (1) or absent (0), SAP numeric systolic arterial pressure, SAP (cat) categorised as normal (0, 110–140 mmHg) or abnormal (1, <110 mmHg or >140 mmHg); VO<sub>2peak</sub>, peak oxygen uptake during maximal exercise.

AIC analyses. Why individuals with greater aerobic capacity would tend to be at higher risk is unclear, and challenges our assumptions about the relationships between physical fitness, VO<sub>2peak</sub> and CVD risk after SCI. It may be that VO<sub>2peak</sub> less strongly reflects physical activity/fitness after SCI, where oxygen consumption is limited by other parameters such as the ability to increase HR or ventilation during exercise, and the active muscle mass. Of note, it was not possible to determine VO<sub>2peak</sub> in many individuals with

high-level lesions who could not complete the exercise test, and who would be expected to have the lowest aerobic capacity and highest CVD risk. It is likely that this bias would have influenced our analyses and might be one additional factor behind the lack of association between low VO<sub>2peak</sub> and high CVD risk. Certainly there are current exercise guidelines [51] for the SCI population aimed at improving aerobic capacity with the goal of improving cardiometabolic risk, but depending on several social, mental and physical factors, these may or may not be feasible for many individuals with SCI. While there are a myriad of benefits to regular physical activity, the efficacy and practicality of the modification of CVD risk through increased physical activity is uncertain at the present time.

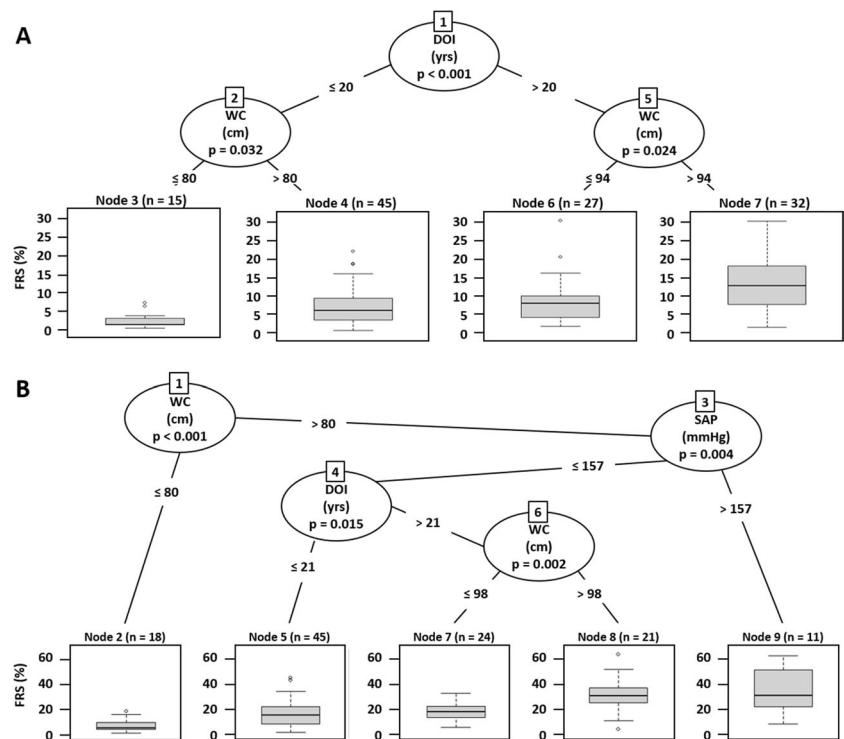
This study considered only traumatic SCI, because of the small number of individuals with non-traumatic SCI in the sample, and the possibility that risk factors may not equate equally across injury subtypes. In general, the demographic data from this cohort compared well with known SCI statistics [2]. However, there was a larger proportion of high LOI in this cohort compared to population averages. There were fewer females than males, and the females in this cohort tended to have a low cardiovascular risk profile (as is the case in the able-bodied), limiting our ability to reliably determine CVD risk cut-points for females and to evaluate sex differences in CVD risk following SCI.

With any analysis approach there are strengths and weaknesses regarding the way covariates or confounding variables are addressed, as well as with how missing values are handled. Some techniques are more suitable for particular data management approaches, and in terms of dissemination of information to different populations (clinicians, patients, etc.) some approaches will be more intuitive. Here we confirmed the rigour of our results by employing several different techniques to evaluate CVD risk factors, including more traditional correlations and regressions, to more novel AIC and URP analyses. This multipronged approach increases our confidence in our findings and recommendations. In particular, our analysis approaches consistently featured the importance of WC, DOI, and autonomic control of HR for the prediction of CVD in individuals with SCI.

We considered a number of clinical metrics that influence CVD risk; however, we did not consider the impact of diet and nutrition on CVD risk. This is important because WC was one of the few modifiable risk factors for individuals with SCI to target improvements in CVD risk. Future studies should investigate the effects of dietary modification and increased physical activity for CVD risk reduction.

Finally, although we noted medication use in our participants, we did not adjust our analyses for medication use, partly because we were not significantly powered to do so, and partly because this was not a focus of our research question. We believe this reflects the clinical reality for

**Fig. 3 Unbiased recursive partitioning (URP) conditional inference tree for CVD risk after traumatic SCI.** The upper part represents significant sequential splits based on early predictors (only significant predictors appear within the tree), while the lower part represents the partition of the initial population as homogenous subgroups. Box plots show the sample size and distribution of FRS within each subgroup. (A) 10-year FRS; (B) 30-year FRS. A multiple testing-adjusted *p* value is given, which gives a statistical description of the strength between the predictors (WC, DOI, SAP) and the outcome measure (FRS). DOI duration of injury, WC waist circumference, SAP systolic arterial pressure, FRS Framingham risk score, *n* sample size.



individuals living with SCI, and the medications used in this study were typical medications taken by individuals with SCI (Supplementary Table 1). However, we recognise that the use of cardiovascular medications in particular might influence the cardiovascular risk scores.

## Conclusions

These data confirm WC as a simple, practical, modifiable measure of CVD risk following SCI. WC is also associated with injury characteristics and impaired autonomic function. We provide cut-points for WC, injury characteristics and autonomic measures for preliminary identification of those who may have an increased risk of an adverse cardiovascular event, providing simple tools that may be used to guide further evaluation and risk management. Furthermore, WC, DOI,  $HR_{peak}$ , and SAP were repeatedly identified as important variables in determining CVD risk. We propose that, whenever possible and in addition to traditional cardiovascular risk factors, measures of autonomic function and WC are determined and used to create a risk profile and guide management of CVD risk.

## Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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**Author contributions** JJC, JKK, MCD and VEC conceived the idea for the study. MWMP and SDG designed the study protocol and collected the data. MCD and VEC analysed the data and interpreted the results. JJC, JKK, MWMP, SDG, TML and VEML assisted in interpreting the results. MCD and VEC wrote the paper. VEC supervised the research. All authors contributed to the critical revision of the paper.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

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